

What is claimed is:

1. A transgenic mouse whose genome comprises at least one transgene comprising a DNA sequence encoding a normal, mutant, or altered gene encoding a protease inhibitor gene operably linked to a promoter effective for expression of said gene
5 in the brain tissue of said mouse.
2. The transgenic mouse of claim 1, further comprising a second transgene operably linked to a promoter effective for expression of said second transgene, in which said second transgene comprises a DNA sequence encoding a normal, mutant, or
10 altered gene encoding tau-i, apolipoprotein E, APP, presenilin 1, presenilin 2, IL-1 alpha, or IL-1 beta.
3. The mouse of claim 1 wherein the promoter is a glial fibrillary acidic protein (GFAP) promoter.
4. The mouse of claim 3 in which said promoter is devoid of ATG start codons.
- 15 5. The mouse of claim 1 wherein the protease inhibitor is antichymotrypsin.
6. The progeny of the mouse of claim 1 wherein the genome of said progeny comprises homozygous or heterozygous alleles of human antichymotrypsin (ACT) gene.
7. A primary cell culture or cell line derived from the mouse of claim 1.
- 20 8. The transgenic mouse of claim 1 in which the expression of said ACT gene produces symptoms of a disease that is essentially similar to a human Alzheimer's disease or amyloidogenic disease.
9. The mouse of claim 8 wherein said amyloidogenic disease is selected from the group consisting of scrapie, transmissible spongiform encephalopathies (TSE's),
25 hereditary cerebral hemorrhage with amyloidosis Icelandic-type (HCHWA-D), hereditary cerebral hemorrhage with amyloidosis Dutch-type (HCHWA-D), Familial Mediterranean Fever, Familial amyloid nephropathy with urticaria and deafness (Muckle-Wells syndrome), myeloma or macroglobulinemia-associated idopathy associated with amyloid, Familial amyloid polyneuropathy (Portuguese),
30 Familial amyloid cardiomyopathy (Danish), Systemic senile amyloidosis, Familial amyloid polyneuropathy (Iowa), Familial amyloidosis (Finnish), Gerstmann-Staussler-Scheinker syndrome, Medullary carcinoma of thyroid, Isolated atrial amyloid, Islets of Langerhans, Diabetes type II, and Insulinoma.

10. A method of screening a compound suspected of having utility for treating Alzheimer's disease or amyloidogenic disease, said method comprising:
providing the transgenic mouse of claim 1;
administering said compound to said mouse; and
5 monitoring a pathological or cognitive marker of said disease.
11. A method of treating or preventing Alzheimer's or amyloidogenic disease, said method comprising administering to a subject in need thereof an effective amount of a pharmaceutically acceptable salt of a compound identified in the screening method of claim 10, in a pharmaceutically acceptable carrier.
- 10 12. A method of screening a compound suspected of inhibiting or promoting phosphorylation of one or more proteins associated with Alzheimer's disease, said method comprising:
providing the transgenic mouse of claim 1;
administering said compound to said mouse; and
15 monitoring the phosphorylation state of said one or more proteins.
13. The method of claim 12 in which said protein is an endogenous mouse tau protein, a product of a human tau transgene or a mitosis specific protein.
14. The method of claim 12 in which said protein is an APP, cdc-2/cyclin B, cdk5, p53, cdc47, MAD, cyclin D, or cyclin E.
- 20 15. A method of screening a compound suspected of inhibiting or promoting formation or aggregation of abnormal protein filaments within a neuron or neuronal process, said method comprising:
providing the transgenic mouse of claim 1;
administering said compound to said mouse; and
25 monitoring the formation or aggregation of said filament.
16. A method of screening a compound suspected of inhibiting or promoting the development of neuronal cell death or synapse loss, said method comprising:
providing the transgenic mouse of claim 1;
administering said compound to said mouse; and
30 monitoring said neuronal cell death or synapse loss.
17. The method of claim 16, in which said neuronal cell death or synapse loss is monitored by TUNEL staining, neurofilament antibody staining, or synaptophysin antibody staining.

18. A method for testing a compound suspected of promoting or inhibiting phosphorylation of one or more proteins related to Alzheimer's disease, said method comprising:

providing a mammalian cell;

5 administering to said cell antichymotrypsin and said compound; and

monitoring the phosphorylation state of said one or more proteins.

19. The method of claim 18 in which said protein is tau, APP, cdc-2/cyclin B, cdk5, p53, cdc47, MAD, cyclin D, or cyclin E.

20. A method for testing a compound suspected of promoting or inhibiting the activity of a protease inhibitor to promote or inhibit cell death or cell division, said method comprising:

providing a mammalian cell;

administering to said cell antichymotrypsin and said compound; and

monitoring cell death or cell division.

21. A method for testing a compound suspected of promoting or inhibiting the activity of a protease inhibitor to promote or inhibit neurite outgrowth, said method comprising:

providing a mammalian neuronal cell;

administering to said cell antichymotrypsin and said compound; and

20 monitoring said neurite outgrowth.

22. The method of claim 18 in which said cell is neuronal.

23. A method of treating or preventing Alzheimer's disease in a patient, said method comprising administering to said patient an effective amount of a pharmaceutically acceptable salt of a compound that is an antichymotrypsin inhibitor in a pharmaceutically acceptable carrier.

24. A method for measuring the effect on cognitive function in a transgenic animal of a compound suspected of having utility in the treatment or prevention of Alzheimer's disease, said method comprising:

30 providing a first group and a second group of transgenic mice that are an animal model of Alzheimer's disease;

administering said compound to each mouse in said first group; and

measuring the cognitive function of each said mouse in said first and second group in
a radial arm water maze having an escape platform capable of relocation among
5 the radial arms of said maze.

25. The method of claim 24 in which each said transgenic mouse further comprises a
normal, mutant, or homologous transgene encoding a protease inhibitor.

26. The method of claim 25 in which said protease inhibitor is antichymotrypsin.

10 27. The method of claim 25 in which said protease inhibitor is anti-trypsin, alpha-2-
macroglobulin, BACE, or a Kunitz inhibitor-containing protein.

28. The method of claim 24 in which said compound suspected of having utility in the
treatment of Alzheimer's disease is an anti-inflammatory agent, an inhibitor of an
interaction between A-beta peptide and antichymotrypsin, an inhibitor of an
15 interaction between A-beta peptide and apolipoprotein E, an inhibitor of
antichymotrypsin expression, an inhibitor of apolipoprotein E expression, an
inhibitor of APP expression, or an inhibitor of expression of an A-beta peptide.